ONLINE SUPPLEMENT TO:

Preventing hypoxemia with manual ventilation during endotracheal intubation: protocol and statistical analysis plan for a multi-center randomized trial

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1. SPIRIT 2013 Checklist

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

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*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

2. Definition of Ventilator Free Days (VFDs)

Ventilator-free days are defined as the number of days on which the patient is alive and breathing without assistance between the patient's final receipt of assisted breathing within the 28 days after enrollment and 28 days after enrollment. If a patient dies before day 28, VFD is 0. If a patient is receiving assisted ventilation at day 28, VFD is 0. If the patient is discharged while receiving assisted ventilation, VFD is 0. Otherwise, VFD is calculated as 28 minus the study day on which the patient ultimately achieved unassisted breathing. All data will be censored at the time of first hospital discharge or 28 days.

3. Definition of ICU-Free Days (ICUFDs)

ICU-free days are defined as the number of days on which the patient is alive and not in an ICU between the patient's final transfer out of the ICU within the 28 days after enrollment and 28 days after enrollment. If a patient dies before day 28, ICU-free days are 0. If a patient is in an ICU at day 28, ICU-free days are 0. Otherwise, ICU-free days are calculated as 28 minus the study day on which the patient was ultimately transferred out of the ICU. All data will be censored at the time of first hospital discharge or 28 days.

4. Adjudication of new infiltrate, pneumothorax, or pneumomediastinum

Exploratory safety outcomes include new infiltrate on chest x-ray in the 48 hours following intubation, new pneumothorax within 24 hours of intubation, and new pneumomediastinum within 24 hours of intubation. The presence of new infiltrate, new pneumothorax, or new pneumomediastinum are determined by independent review of chest imaging by two pulmonary and critical care medicine attending physicians at the coordinating center who are unaware of study group assignment. Each site provides the coordinating center the most recent chest x-ray prior to intubation and all chest x-rays obtained between intubation and 48 hours after intubation. Each film is de-identified and reviewed independently by two pulmonary and critical care medicine attending physicians who are unaware of study group assignment. The presence or absence of new infiltrate, new pneumothorax, or new pneumomediastinum is recorded using a standardized data collection sheet. If a pre-intubation chest x-ray is not available, any infiltrate, pneumothorax, or pneumomediastinum is considered to be new. Any assessments that are discordant between the two independent reviewers are resolved by independent, blinded review by a third pulmonary and critical care medicine physician.

5. Initial Sample Size Calculation

The initial sample size calculation was made using data from previous prospective trials enrolling a similar population of patients in similar ICUs. These trials demonstrated a standard deviation of 14% in the primary outcome of lowest arterial oxygen saturation.[1] The difference between groups in lowest arterial oxygen saturation felt to be clinically meaningful in prior trials was 5%.[2–4] Using PS version 3.1.2 with the above assumptions and a two-sided alpha level of 0.05, we calculated that achieving a statistical power of 90% would require enrollment of 332 patients. Anticipating up to 5% missing data for the primary outcome, enrollment of a total of 350 patients was planned.

6. Sample Size Re-estimation

The trial protocol and DSMB charter specified that the DSMB would recommend sample size re-estimation at the interim analysis if the standard deviation for lowest oxygen saturation in the control arm was larger than 14%, in order to prevent the final study from being underpowered to detect the planned difference between groups in lowest oxygen saturation. At the interim analysis, the observed standard deviation for lowest oxygen saturation in the control arm was 15%. Using nQuery Advisor® version 7.0, we calculated that maintaining a statistical power of 90% to show a difference of 5% in lowest oxygen saturation with a standard deviation of 15% and a two-sided alpha level of 0.05 would require enrollment of 380 patients. Anticipating up to 5% missing data for the primary outcome, enrollment of a total of 400 patients would be required. Based on these calculations, the DMSB recommended increasing the final planned sample size to 400 patients.

To understand the ability of the updated sample size to inform the assessment of the safety of the intervention, we conducted exploratory sample size calculations for the safety outcomes. The main safety outcomes are lowest oxygen saturation, highest fraction of inspired oxygen (FiO2), and highest positive end-expiratory pressure (PEEP) from 6 to 24 hours after intubation between the two study groups. In the 24 hours following intubation in a prior trial in a similar population, the standard deviation in lowest oxygen saturation was 11%, the standard deviation in highest FiO2 was 0.33, and the standard deviation in highest PEEP was 3.3 cmH_2O.[28] By enrolling 400 patients, we estimated that we would have 80% statistical power at an alpha of 0.05 to detect a 3.1% difference between groups in the lowest oxygen saturation in the 24

hours after intubation, a 0.09 difference in the highest FiO2, and a 0.9 cmH_2O difference in highest PEEP.

The exploratory safety outcomes are less common clinical events than the primary outcome and the main safety outcomes. Operator-reported aspiration has occurred in prior trials at an incidence of 1.0-6.0%. Therefore, enrollment of 400 patients would provide 80% statistical power at an alpha level of 0.05 to detect an absolute difference in the incidence of aspiration between groups of 6.0-10.5%. New infiltrate on chest imaging following intubation has been reported in prior studies to occur with an incidence of 4-8%.[1,29] Enrollment of 400 patients would provide 80% power at an alpha level of 0.05 to detect an absolute difference between groups of 8.1-9.9%, respectively.

7. Data and Safety Monitoring Board Charter

DATA AND SAFETY MONITORING BOARD CHARTER

Charter, Data and Safety Monitoring Board for

"Preventing Hypoxemia with Manual Ventilation during endotracheal intubation (PreVent) Trial"

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Confidential Information

The information contained within this Charter is confidential and intended for the use of the DSMB

_____

DSMB Member Printed Name

_____ _____

DSMB Member Signature Date

Charter, Data and Safety Monitoring Board for

Preventing Hypoxemia with Manual Ventilation during endotracheal intubation (PreVent) Trial

January 2017

1. Introduction

This Charter is for the Data and Safety Monitoring Board (DSMB) for the Preventing Hypoxemia with Manual Ventilation during endotracheal intubation (PreVent) Trial

The Charter is intended to be a living document. The DSMB may wish to review it at regular intervals to determine whether any changes in procedure are needed.

2. Responsibilities of the DSMB

The DSMB is responsible for safeguarding the interests of study participants, assessing the safety and efficacy of study procedures, and for monitoring the overall conduct of the study.

The DSMB is an independent group advisory to the sponsor of this trial, Matthew W Semler, MD, MSc and is required to provide recommendations about starting, continuing, and stopping the trial. In addition, the DSMB is asked to make recommendations, as appropriate, to the investigators about:

- Benefit/risk ratio of procedures and participant burden
- Selection, recruitment, and retention of participants
- Adherence to protocol requirements
- Completeness, quality, and analysis of measurements
- Amendments to the study protocol
- Performance of individual centers
- Participant safety
- Notification of and referral for adverse events

3. Organization and Interactions

Communication with DSMB members will be primarily through Dr. Semler. It is expected that study investigators will not communicate with DSMB members about the study directly, except when making presentations or responding to questions at DSMB meetings or during conference calls.

4. DSMB Members

DSMB members and their expertise are listed in Appendix A. The DSMB consists of two physicians experienced in critical care, the conduct of clinical trials including data and safety monitoring, and have formal training to conduct statistical analyses necessary for the planned interim analysis. Dr. Semler or his designee will serve as the Executive Secretary (ES) and be responsible for keeping the minutes of the open sessions. The Chair of the DSMB will be responsible for recording the minutes of the closed sessions and for the timely transmission of the final DSMB recommendations to Dr. Semler. Dr. Semler will be responsible for the timely notification of investigators of all DSMB recommendations.

5. Scheduling, Timing, Content, and Organization of Meetings

DSMB meetings will be held by teleconference. The purpose of the first meeting is to review and discuss this Charter and the study protocol, including the Data Safety Monitoring Plan. Dr. Semler or his designee can conduct this meeting with individual DSMB members or as a group. Enrollment in the study cannot begin until Dr. Semler has accepted the DSMB's recommendation for approval and IRB approval has been obtained. All DSMB members must sign and return the charter to Dr. Semler or his designee to indicate their approval.

Conference calls are to be held approximately twice a year, with additional conference calls scheduled as needed. Conference calls will be scheduled by Dr. Semler or the ES in collaboration with the DSMB members.

The DSMB will review 30-day data after 175 subjects have been enrolled; enrollment will continue during DSMB review. The primary focus of this review will be efficacy and safety. All data will be supplied to the DSMB with blinded treatment groups; however, the DSMB will be able to request unblinding for any reason. All serious adverse events thought to be related to study procedures will be reported to the DSMB on an ongoing basis; the study will be stopped for a safety evaluation by the DSMB if they have any concerns based on either the interim data analysis or review of serious adverse events.

The agenda for DSMB meetings and calls will be drafted by Dr. Semler. Dr. Semler will finalize the agenda after consultation with the DSMB Chair. The agenda and meeting materials should be distributed by the ES two weeks before each call.

Before each teleconference the ES will ask all DSMB members to state whether they have developed any new conflicts of interest since the last call. If a new conflict is reported, the Chair will determine if the conflict limits the ability of the DSMB member to participate in the discussion.

It is expected that all DSMB members will attend every call and respond to electronic mail communications promptly. A quorum of this DSMB will be all two members.

6. Discussion of Confidential Material

DSMB meetings and calls will be organized into open, closed, and executive sessions.

- During the **open sessions**, Dr. Semler will present information to the DSMB on behalf of the study investigators with time for discussion.

- During the **closed sessions**, the DSMB will discuss confidential and/or unblinded data from the study. Steps will be taken to ensure that only the appropriate participants are on the call, and to invite others to re-join the call only at the conclusion of the closed session.

- The DSMB may elect to hold an **executive session** in which only the DSMB are present in order to discuss study issues independently. Voting on recommendations will follow Roberts' Rules of Order (**Robert's Rules of Order Newly Revised (10th Edition) RONR** by Henry M. Robert III, William J. Evans (Editor), Daniel H. Honemann (Editor), Thomas J. Balch (Editor), Sarah Corbin Robert, Henry M. Robert III, General Henry M. Robert). If the executive session occurs on a conference call, steps will be taken to ensure that only the appropriate participants are on the call, and to invite others to re-join the call only at the conclusion of the executive session.

At the conclusion of the closed and executive sessions, the participants will be re-convened so that the DSMB Chair can provide a summary of the DSMB's recommendations. This provides an opportunity for study investigators to ask questions to clarify the recommendations. The meeting is then adjourned.

7. Reports of DSMB Deliberations

- Initial summary: The ES is responsible for assuring the accuracy and transmission of a brief summary of the DSMB's discussion and recommendations. Dr. Semler will review this summary and approve or disapprove the recommendation(s), or request additional information. The recommendations will then be sent to the clinical investigators.

- Action plan: If the DSMB's recommendations require significant changes or follow-up, Dr. Semler will prepare an action plan outlining the steps required to implement the recommendations.

- Formal minutes: The ES is responsible for the accuracy and transmission of the formal DSMB minutes within 30 days of the meeting or call. These minutes are prepared accordingly to summarize the key points of the discussion and debate, requests for additional information, response of the investigators to previous recommendations, and the recommendations from the current meeting. The DSMB Chair may sign the minutes or indicate approval electronically via email.

8. Reports to the DSMB

For each meeting, Dr. Semler will prepare summary reports and tables to facilitate the oversight role of the DSMB. The DSMB will discuss at the first meeting what data they wish to review and how it should be presented. Data requests can be modified at subsequent meetings.

9. Statistical Monitoring Guidelines

At the first meeting, review of the protocol will include review of the clinical endpoints and safety monitoring plans. The DSMB should discuss the adequacy of that plan. The DSMB should discuss the statistical monitoring procedures they propose to follow to guide their recommendations about termination or continuation of the trial. The DSMB should discuss the statistical monitoring procedures they propose to follow to guide their recommendations about termination or continuation of the trial.

10. Stopping Rules

At the meeting for the planned interim analysis (at least 30 days after enrollment of 175 patients), the DSMB will be provided the following blinded data in raw format:

1. Study group assignment of each patient (A vs B)
2. Lowest arterial oxygen saturation during the procedure
3. Lowest arterial oxygen saturation in the 24 hours following intubation
4. Highest fraction of inspired oxygen in the 24 hours following intubation

5. Highest positive end expiratory pressure in the 24 hours following intubation
6. Mortality
7. Ventilator-free days

At this interim analysis, the DSMB will be asked to perform 2 analyses using these data: a efficacy analysis and safety analysis as described below. At the completion of these analyses, the DSMB will notify Dr. Semler if the trial should be stopped for any of these three reasons or continued to completion. The DSMB will not make Dr. Semler or any of the investigators aware of the results of any of their analyses. At the interim analysis or at any other time where the DSMB is deciding if the trial should be stopped or continued, all of the members of the DSMB must agree that the trial should be stopped or continued.

11. Efficacy Stopping Rules

The DSMB will conduct a single interim analysis for efficacy at the anticipated halfway point of the trial, 30 days after enrollment of 175 patients. Enrollment will continue during this period. The **stopping boundary for efficacy** will be met if the *P* value for the difference between groups in the primary outcome is 0.001 or less. Use of the conservative Haybittle-Peto boundary ($P < 0.001$) will allow the final analysis to be performed using an unchanged level of significance ($P = 0.05$). Given the minimal risk nature of the study and current use of both interventions as a part of usual care, there will be **no stopping boundary for futility**.

12.Safety Stopping Rule

With regards to safety, the DSMB will be able to stop study accrual at any time if there is concern for safety. Other than these concerns, the DSMB will be asked to formally evaluate the safety of the trial at the interim analysis described above 30 days after enrollment of 175 patients. The primary determination of safety will be based on the highest fraction of inspired oxygen and highest positive end-expiratory pressure between 6 and 24 hours after intubation. The **safety stopping boundary** is as follows:

1. The *P* value for the difference between study groups in both of these physiologic variables is < 0.001, AND
2. The difference between groups in both physiologic variables is concordant in direction with the point estimate for in-hospital mortality, AND
3. The *P* value for the difference between study groups in in-hospital mortality is < 0.1

The DSMB will also be provided with blinded data on all outcomes collected by the trial to use in their review of trial safety. Additionally, the DSMB will reserve the right to stop the trial at any point, request additional data or interim analyses, unblind the study assignments, or request modifications of the study protocol as required to protect patient safety. Finally, the DSMB will have the ability to monitor the standard deviation of the primary outcome in the

control group at the interim analysis and can ask that the study be re-powered if the standard deviation of the primary outcome is different from our original estimate of 14%. This standard deviation will be calculated by the investigators and given to the DSMB in a blinded fashion.

8. Plan for communication of protocol changes

Any changes to the trial protocol (eg, changes to eligibility criteria, outcomes, analyses) will require a new version of the full trial protocol which will be tracked with the date of the update and the version number of the trial protocol. A list summarizing the changes that are made with each protocol revision will be included at the end of each protocol. The updated protocol will be sent to the Vanderbilt IRB for tracking and approval prior to implementation of the protocol change. At the time of publication, the original trial protocol and the final trial protocol, including the summary of changes made with each protocol change, will be included in the supplementary material for publication.

9. Patient Privacy and Data Storage

At no time during the course of this study, its analysis, or its publication will patient identities be revealed in any manner. The minimum necessary data containing patient or provider identities is collected. All patients are assigned a unique study ID number for tracking. Data collected from the medical record is entered into the secure online database REDCap. Hard copies of the data collection sheet completed at the time of the airway management event are stored in a locked room until after the completion of enrollment and data cleaning. Once data are verified and the database is locked, all hard copies of data collection forms will be destroyed. All data is maintained in the secure online database REDCap until the time of study publication. At the time of publication, a de-identified database will be generated.